9th CONGRESS OF THE EUGMS
European Union Geriatric Medicine Society
IMPROVING OUTCOMES IN GERIATRIC MEDICINE

Flu vaccination in populations with cardio/neurovascular risk factors

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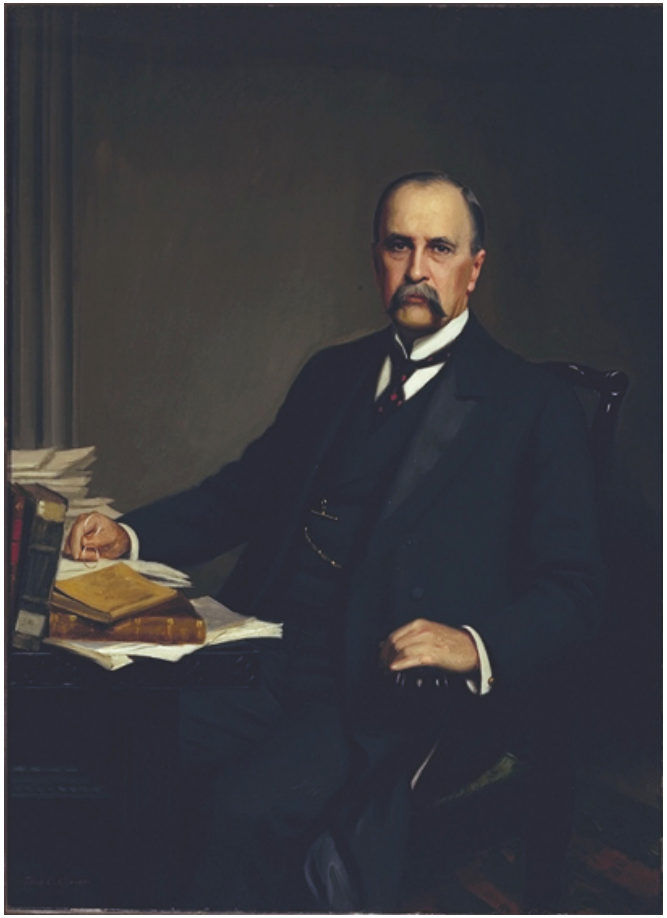
Infection and coronary heart disease

William Osler 1849-1919



Influenza mortality in patients at risk

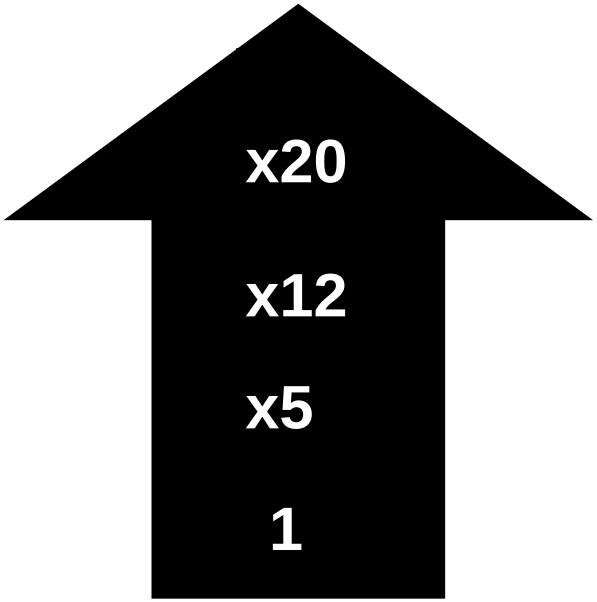
Deaths from influenza or pneumonia

Associated cardiovascular & pulmonary disease

Pulmonary disease

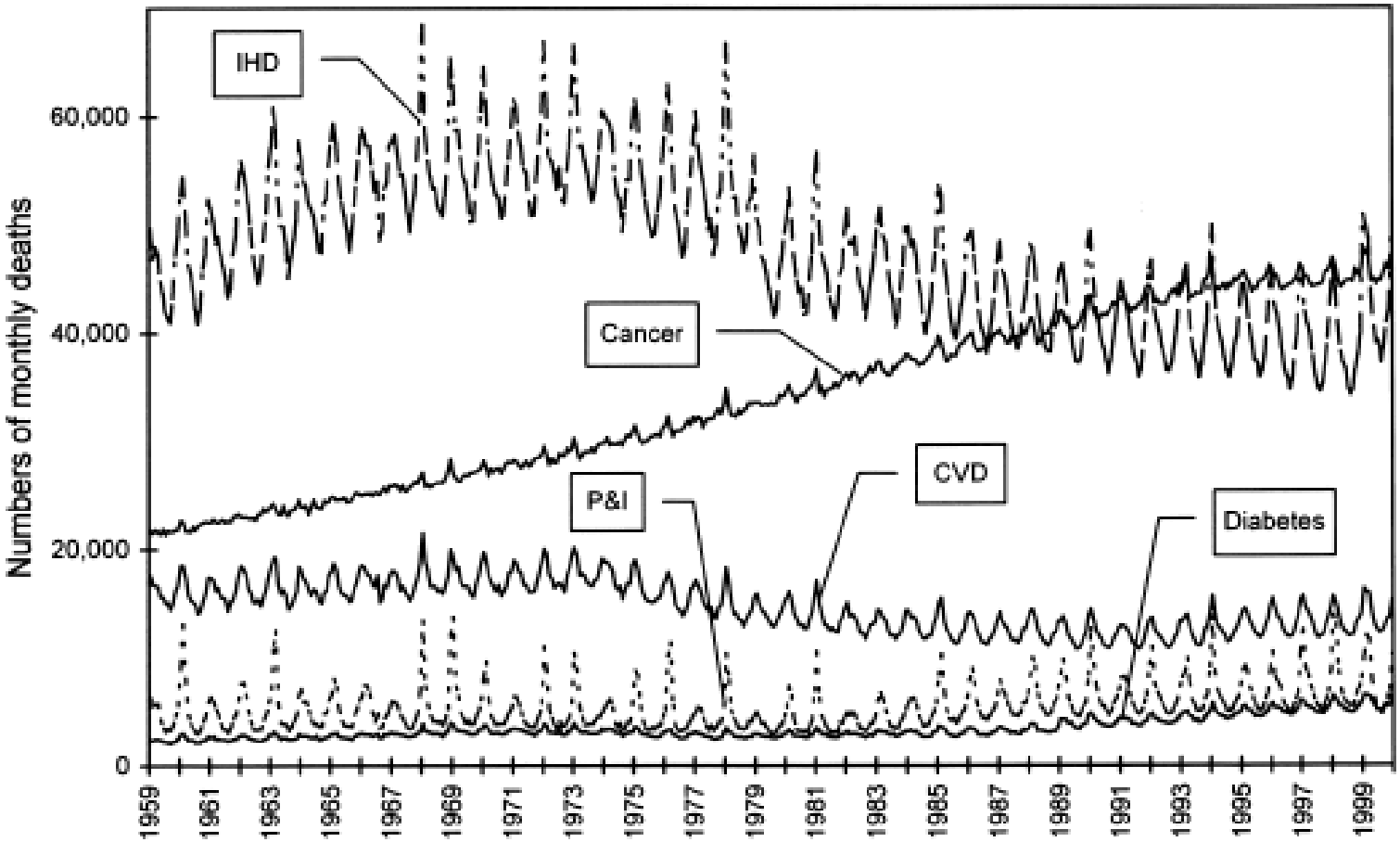
Cardiovascular disease

Healthy adults: 36/100,000



Schanzer Vaccine 2008 26:4697–4703

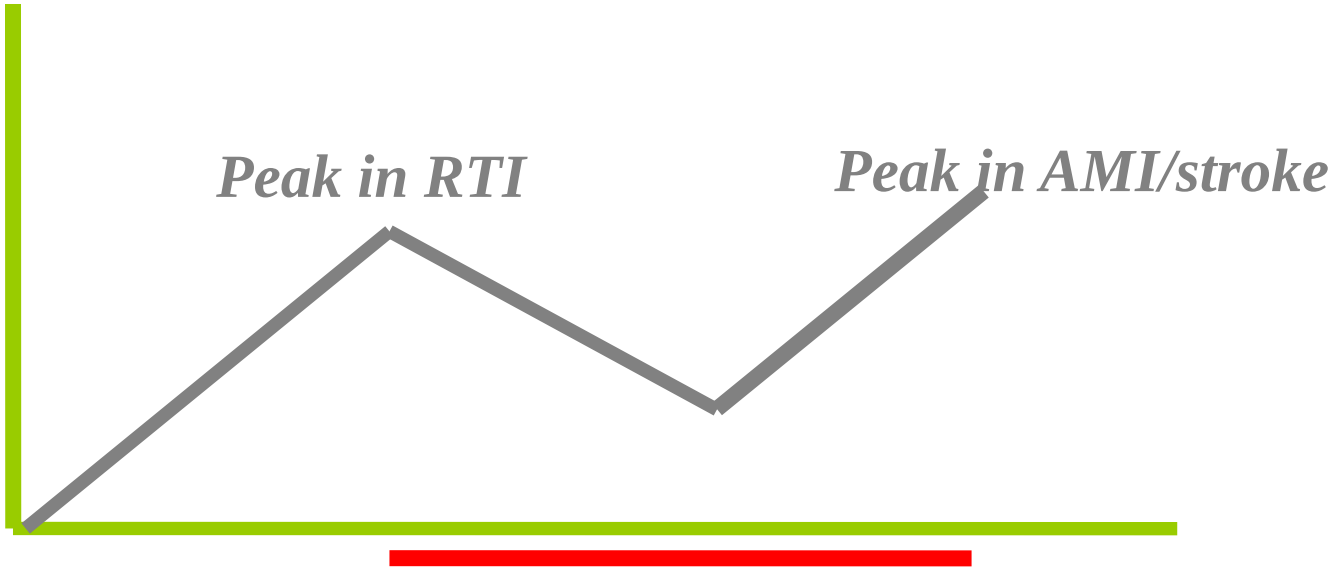
Winter mortality and influenza



Reichert Am J Epidemiol 2004;160:492–502

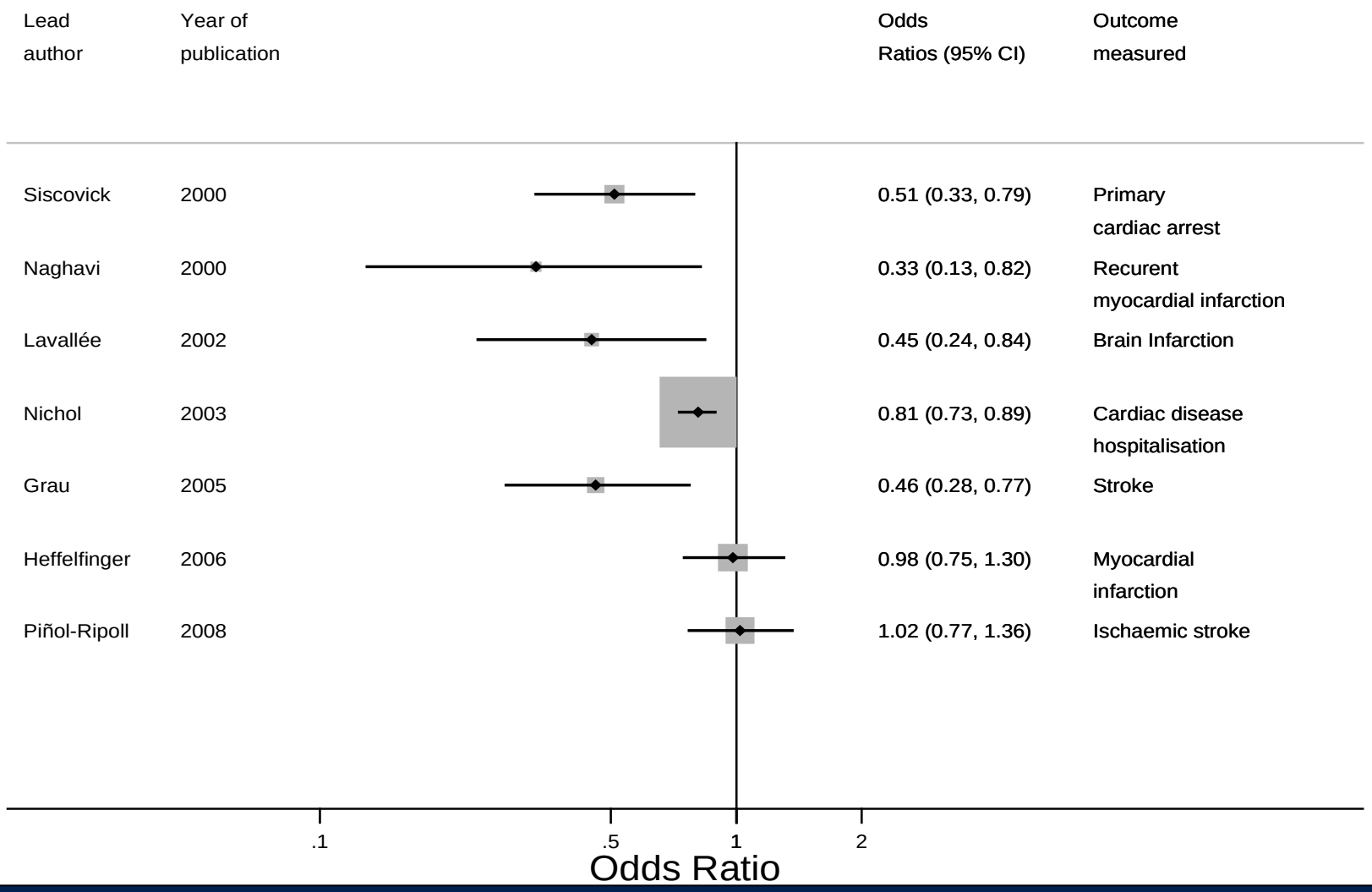
Wong PLoS Med 2006 3(4):e121.

Respiratory infection precedes AMI/stroke



Clayton, Thompson & Meade Eur Heart J 2008:29: 96-103
Smeeth et al. NEJM 2004; 351: 2611-2618
Meier et al. Lancet 1998:351: 1467-1471
Spodick et al. Am J Cardiol 1984:53: 481-482.

Influenza vaccination and AMI/stroke



Pneumococcal vaccination and AMI

- Case control study
- Pneumococcal vaccination was associated with a decrease of more than 50% in the rate myocardial infarction 2 years after exposure.

Lamontagne et al. CMAJ 2008:179: 773-777

Previous studies

- Contradictory evidence
- Bias: recall, therapeutic
- Confounding: ‘healthy user effect’

Study aims

To investigate association of influenza & pneumococcal vaccination for AMI or stroke using GPRD/CPRD and using

a. Matched case-control design
b. Self-controlled case series design

Methods: case-control

- Matched case-control design
- AMI: 1/11/2001 – 31/05/2007
- Stroke: 1/9/2001 – 31/8/2009
- Outcome: first AMI or stroke (fatal or non-fatal)
- Exposure
  - prior influenza vaccination (≤ 1 year, within season)
  - prior pneumococcal vaccination (ever)
  - combined vaccination
- Inclusion:
  - ≥ 40+ years at incident diagnosis
  - ≥ 5 years of complete follow-up data
  - alive from beginning of study to index date
  - at least one matching case or control

Methods: case-control

- ‘Case: Read/OXMIS codes of first AMI
- ‘Index date’: first date when GP recorded AMI/stroke code (fatal/non-fatal) in clinical/referral record
- ‘Control’: 4 (AMI) or 1(stroke) age/sex matched controls per case with index date corresponding to date of matched case

Analysis: case-control

- STATA: conditional logistic regression
- Outcomes: adjusted odds ratios
- Confounding factors considered for adjusted OR
  - Vaccine risk groups: chronic heart (and other cardiovascular diseases); diabetes, asthma/COPD; chronic renal and liver disease; splenectomy
  - Other CHD risk factors: smoking status; hyperlipidaemia; BMI; family history of AMI; antihypertensive treatment, recent aspirin or statin therapy
  - Frequency of GP visits (frailty/disability)
  - [Comorbidities]

Descriptive statistics: AMI

		Cases (AMI) N=16 012	Control N=62 694	Overall N=78 706
Age (years):	Mean (SD)	70.4 (12.7)	70.0 (12.5)	70.1 (12.6)
	95% CI	70.2 – 70.6	69.9 – 70.1	70.0 – 70.2
Aged over 65 years (%)		66.6	65.9	66.1
Gender:	Male (%)	61.5	61.5	61.5
Index period:	Dec – Feb	29.1		
	Mar – May	26.0	--	--
(%)	Jun – Aug	21.6		
	Sep – Nov	23.3		

Descriptive statistics: stroke

		Cases (those with stroke/TIA) N= 47,216 (%)	Controls N= 47,216 (%)
Age (years):	Mean (SD)	79.8 (13.4)	79.8 (13.4)
	95% CI	79.7 – 80.0	79.7 – 80.0
Aged over 65 years		76.8	76.8
Gender:	Male	48.0	48.0
Index period:	Sep – Nov	24.6	
	Dec – Mar	33.9	--
	April – Aug	41.5	

Vaccine risk groups	Case N=16 012 *n(%)*	Control N=62 694 *n(%)*	p
Asthma or COPD	1980 (12.4)	5803 (9.3)	<0.001
Chronic heart disease	3756 (23.5)	6174 (9.9)	<0.001
Other vascular diseases	1280 (8.0)	2956 (4.7)	<0.001
Diabetes	2451 (15.3)	5637 (9.0)	<0.001
Splenectomy	36 (0.2)	116 (0.2)	0.306
Chronic liver disease	30 (0.2)	93 (0.2)	0.265
Chronic renal disease	584 (3.7)	724 (1.2)	<0.001

Cardiovascular risk factors	Case N=16 012 (%)	Control N=62 694 (%)	P
Hyperlipidaemia	13.6	9.3	<0.001
Smoking history			
Never smoked	41.7	54.4	<0.001
Ex-smoker	30.1	27.6	
Current smoker	28.2	18.0	
Body mass index ≥ 25	63.2	59.5	<0.001
Family history of MI	1.9	1.5	0.001
Aspirin	0.4	0.2	<0.001
Statin	11.4	7.0	<0.001
Antihypertensive treatment	6.5	3.9	<0.001
+GP consultations in last 5 years: 27 +	57.7	46.2	<0.001

Main results: AMI case-control

Timing	Cases N(%)	Controls N(%)	Adjusted	
			OR	95% CI
Within season	7496 (46.8)	28487 (45.4)	**0.80**	**0.76-0.84**
Early within-season (Sept. to mid-Nov.)	6770 (42.3)	25911 (41.3)	**0.79**	**0.75-0.83**
Late within-season (mid-Nov. to Feb.)	726 (4.5)	2571 (4.1)	**0.88**	**0.79-0.97**

Main results: stroke case-control

Timing of Vaccination	Cases N(%)	Controls N(%)	Adjusted	
			OR	95% CI
Same season as index date	13,668 (50.6)	13,709 (50.8)	**0.81**	**0.77 – 0.85**
Early within-season (Sept. to mid-Nov.)	11,995 (44.4)	12,258 (45.4)	**0.79**	**0.75 – 0.84**
Late within-season (mid-Nov. to Feb.)	1,,673 (6.2)	1,451 (5.4)	0.97	0.88 – 1.06

Main results: pneumococcal vaccine

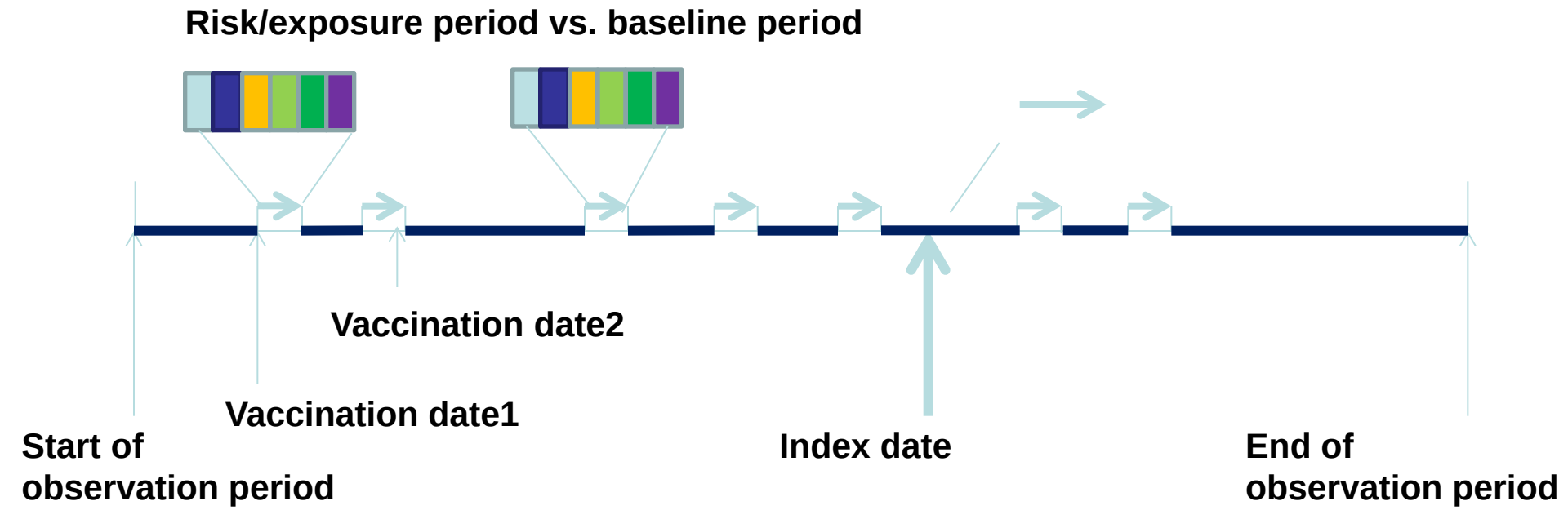
- AMI - Pneumococcal: adjusted OR 0.96 95% CI 0.91 to 1.02
- Stroke - Pneumococcal: adjusted OR 0.97 95% CI 0.92 to 1.02
- Combined influenza and pneumococcal vaccination was no better than influenza vaccination alone

Study strengths and limitations

- Residual confounding (unknown factors)
- ‘Healthy vaccination’ bias
- Incomplete recording of blood pressure, cholesterol levels, height, etc. on the GPRD

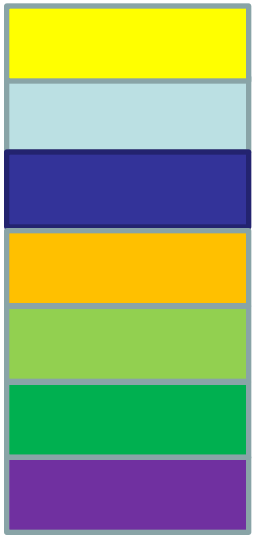
Method: self controlled case series

Observation period 2001-2007 (AMI)/2001-2009 (stroke)



Method: self controlled case series

Exposure/risk periods



14 days pre-vaccination

14 days post-vaccination

15 -28 days post-vaccination

29 - 59 days post-vaccination

60 -90 days post-vaccination

91-120 days post-vaccination

121-180 days post-vaccination

Method: self controlled case series

- 1-14 days pre-vaccination considered as a separate interval: a stroke/TIA event occurring during this period is likely to affect the subsequent likelihood of receiving an influenza vaccination.
- Seasonality was included by dividing the risk periods into one of four quarterly seasons: Sept. to Nov., Dec. to Feb., March to May and June to Aug.

Analysis: self controlled case series

- The incidence rate of AMI/stroke in exposure periods after vaccination compared with the incidence rate during a baseline period.
- Statistical modelling with conditional Poisson regression in Stata 12 was employed to compute incidence rate ratios (IRR).

Sample

- First cases of AMI (14k) or stroke/TIA (40k) within the observation period
- Excluded cases that either did not receive influenza vaccination or have a AMI/stroke diagnosis on or before the vaccination date

Descriptive statistics

- 8 180 of AMI considered for the final analysis.
- 38 674 cases of stroke/TIA considered for the final analysis.

Main results: AMI and flu vaccination

Risk period	Number of cases		Time at risk (person years)	IRR	Adjusted 95% CI
	N	%			
Baseline period	3913	47·8	16898	1·00	-
Post Vac 1-14 days	275	3·4	**1413**	**0·68**	**(0·60 - 0·78)**
15-28 days	289	3·5	**1410**	**0·75**	**(0·66- 0·86)**
29-59 days	703	8·6	**3106**	**0·82**	**(0·75 - 0·90)**
60-90 days	826	10.1	3073	0·96	(0·87 - 1·07)
91-120 days	762	9·3	2926	0·98	(0·89 - 1·09)
121-180 days	1273	15·6	5290	1·02	(0·95 – 1·10)

[a] Adjusted for seasonality
[b] IRR incidence rate ratios.
[c] Baseline is between 180 days or 30th of April (whichever came first) after vaccination and 14 days prior to next vaccination

Main results: stroke and flu vaccination

Risk period	Number of cases		Time at risk (person years)	IRR	Adjusted 95% CI
	N	%			
Baseline period	24,333	62·9	173926	1·00	-
Post vac 1-14 days	1,084	2·8	**8270**	**0·88**	**(0·82 - 0·94)**
15-28 days	1,040	2·7	**7695**	**0·91**	**(0·85 - 0·97)**
29-59 days	2,184	5·7	**16776**	**0·86**	**(0·82 - 0·90)**
60-90 days	2,444	6·3	**17324**	**0·92**	**(0·87 - 0·96)**
91-120 days	2,315	6·0	**16194**	**0·94**	**(0·89 - 0·98)**
121-180 days	4,332	11·2	30525	0·96	(0·93 – 1·00)

[a] Adjusted for seasonality
[b] IRR incidence rate ratios.
[c] Baseline is between 180 days or 30th of April (whichever came first) after vaccination and 14 days prior to next vaccination

Study strengths and limitations

- Large, representative and robust research database with sufficient power to detect effects with precision.
- Selection bias minimized by including all cases of AMI or stroke within the selected time period.
- Method accounts for unknown and known confounders assuming no/little change over the observational period.

Conclusions

- Influenza vaccination associated with reduced risk of AMI and stroke
- Early influenza seasonal vaccination (September to mid-November) associated with lower rate of AMI or stroke than later vaccination (mid-November to January)
- Pneumococcal vaccination not associated with a reduction in rate of AMI or stroke

Siriwardena AN, Gwini S, Coupland C. infarction CAMJ2010; 182 (15): 1617- 1623
Gwini SM, Coupland C, Siriwardena AN. Vaccine 2011; 29: 1145-1149

Implications for practice

- Reinforce recommendations: + younger people (40-64) at risk
- Timing: early vs. late vaccination?

Implications for future research

- Mechanism:?Virchov's triad
- Efficacy trial?

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Thank you!

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